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09/819,401	03/27/2001	Laurent Humeau	397272000700	3802

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EXAMINER
LI, BAO Q

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 04/19/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/819,401	Applicant(s) HUMEAU ET AL.	
	Examiner Bao Qun Li	Art Unit 1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 February 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *9* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: sequence letter

DETAILED ACTION

Claims 1-7 are pending.

The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1648.

Sequence requirements

This application contains sequence disclosures on page 69 to 71 that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Full compliance with the sequence rules is required in response to this Office Action. A complete response to this office action should include both compliance with the sequence rules and a response to the Office Action set forth below. Failure to fully comply with **both** these requirements in the time period set forth in this office action will be held non-responsive.

Information Disclosure Statement

The information disclosure statement filed on paper No. 6, 01/15/2002, fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each U.S. and foreign patent; each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. The references that we can not found in the files or we can not found in the data base have been placed in the application file, but the information referred to therein has not been considered.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is vague and indefinite in that the metes and bonds of cited "viral DNA", "a virus" and "a viral vector" are not defined. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Furthermore, it is unclear whether the virus and viral DNA as well as the viral vector are intended to be the same virus or a different one. If Applicants wish to claim a particular virus and a particular viral vector, the claim should point out which vial vector and virus is intended in the claim. This affects the dependent claim 2-7.

Claim 2 is confusing in that which viral DNA is integrated into the cell genome is unclear. Please clarify.

Claim 7 is vague and indefinite in that the metes and bonds of "a gene" are not defined. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Is a herpes-virus TK gene intended?

Claim 7 is vague and indefinite in that the metes and bonds of the cited " one or more first nucleotide sequences" are not defined. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). If Applicants wish to claim a unique sequence, please amend the claim to a precise sequence that is intended in the claim.

Claims 1-7 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential structural cooperative relationships of elements, such omission amounting to a gap between the necessary structural connections. See MPEP § 2172.01. The omitted structural cooperative relationships are: when the sensitivity and resistance is tested and how it is tested, how to determine the cell has a viral DNA or viral vector DNA genomes integration, what is the relationship between the helper virus or helper vector in regarding to the viral vector, and how to determine the inhibition of the production of the viral DNA by the said viral vector but not by other factors because

if the viral vector is derived form the same the same virus, the antigenicity of the vector itself can produce some immunity to against its progenitor virus in the host also.

Claims 7 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: one or more first nucleotide sequence that are fundamentally important to carry out the invention for using a viral vector to differentially inhibit a wild-type virus replication as well as the helper vector or helper virus replication are missing and how this deferential inhibition is structurally and functionally processed.

Claim Rejections - 35 USC § 112

Claims 1-7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for constructing a conditionally replicating HIV vector (crHIV) comprises a ribozyme cassette for expressing ribozyme molecule(s) encoded by SEQ ID NO: 3 or 4 in either single, double or triple tandem repeats, which is able to cleavage the wild-type HIV virus or helper virus or helper vectors, but not the vector in an in vitro cell line sitting system, does not reasonably provide enablement for having a method for preventing or inhibiting any or all viral DNA replication by using any or all viral vector with comprising any or all kind of nucleotide sequences in vitro as well as in vivo. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The test of scope of the enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art would undue experimentation (See United States v. Theketronic Inc., 8USPQ2d 1217 (fed Cir. 1988). Whether undue experimentation is required is not based upon a single factor but rather a conclusion reached by weighting many factors. Theses factors were outlined in Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and gain in re Wands, 8USPQ2d 1400 (Fed. Cir. 1988).

The method for using ribozyme carried by various vector to inhibit the viral replication or selecting different vector that are suitable for delivery of the ribozyme is

known in the art. The inhibition of the HIV-1 by ribozyme targeting at certain consensus sequence of the HIV-1 genome and the riobozyme that are carried by different vectors in vitro or on vivo as well as in the phase I clinical trail is known in the art as evidenced by Rossi et al. (Adv. Drug Deliv. Rev. 2000, Vol. 44, pp. 71-78, see entire document), and Macpherson et al. (Frontiers in Bioscience, June 1999, pp. 497-505, see entire document). In particular, the method for constructing a HIV-1 based conditional replication vector (crHIV) to expressing anti-HIV ribozyme and inhibit the wild-type HIV-1 replication in an in vitro CD4 + cells are fully disclosed by one of the invention as evidenced by Dropulic et al. (US Patent No. 5,885,806A).

However, this approach has not been reported successfully to be used for HIV-1 infected patients or other viral infection in clinic yet. Because this is related to the gene therapy, therefore, there are several major problem that has not been fully addressed or overcome yet , which problems are associated with efficient delivery to target cells, long term expression and efficient intracellular function have not been addressed as described supra by Rossi et al (Advanced Drug Delivery Reviews 2000, Vol. 44, pp. 71-78, see the section of conclusion on page 76) and Marpheson et al. (Frontiers in Bioscience, June 1999, pp. 497-505, see section 3.3).

Other unpredictability is also addressed by Sarver et al. (AIDS Research and Human Retoviruses 1003, Vol. 9, pp. 483-487, especially in lines 4-17 on right col. of page 486, see lines 4-17 on right col. of page 486). They indicate that although the data for inhibiting the HIV-1 by transient expression of ribozyme in a tissue culture cell line has been reported in the art, the field is still highly unpredictable because it only worked in a transient expression system of a cell line and it may only be sensitive for certain strain of the virus. They further address that the ribozyme approach is imperative to extend to a stable expression system using PBLs, peripheral blood mononulclear cells (PBMCs), and clinical viral isolation because it reported that a lower inhibition level of HIV in PBLs relative to established cell lines.

Because the claimed invention is related to the use of viral vector for treating viral infection, especially for treating the same progenitor virus related infection (crHIV vector/wild-type HIV), it is highly unpredictable whether the vector used is able to produce a replication competent virus because most viruses, such as herpes simplex virus

(HSV), human papiloma virus (HPV) and HIV, which are used for constructing viral vectors, are all associated with latent or non-symptomatic infection in the host. There is a safety concern as well as other ethical/social implication as discussed by Anderson (Science 1992, Vol. 256, pp. 808-813, see lines 32-62 in middle col. and lines 1-62 in the left col. on page 812).

The specification of the instant Application only teach how to construct a condition replication HIV-1 based vector, which comprising a ribozyme expression cassette carrying an anti-HIV ribozyme molecule encoded by SEQ ID NO: 3 or 4 and the specific mutation at several optional ribozyme binding sites in order to avoid the cleavage the crHIV vector itself during the co-inoculating the crHIV vector with the wild-type HIV-1 virus as well as the helper virus or helper vector in an in vitro cell line testing system.

However, Applicants lack the teaching whether the said crHIV vector carrying the anti-HIV ribozyme can produce a sustained anti-HIV ribozyme expression in an in vivo setting system and there is also a deficient about whether the HIV-1 infection can be prevented or inhibited in an in vivo setting system either. The specification does not teach anything regarding to the generation of retroviral replication competent virus if the crHIV is con-inoculated with a wild-type virus because of the homologous recombination between the wild-type HIV and crHIV vector.

The full scope of the invention broadly read on use the gene therapy approach for inhibiting and preventing any or all viral DNA replication in vivo. However, Applicants only presents that the crHIV vector derived form pNL4-3 strain with a limited disclosure of the ribozyme sequence inserted in the vector (SEQ ID NO: 3 or 4) and the substitutive mutation site bound to HIV U5' region, that are tested in vitro only.

Applicants do not teach how to construct other viral vector and insert other nucleotide sequence that is used to inhibit other viral DNA replication.

Considering the large scope of the claimed invention and the difficulty as well as the unpredictability of the filed, significant hurdles remain to be overcome in order for the skilled artisan to practice successful a gene therapy for inhibiting or preventing viral replication by any or all viral vector, it concluded that a skilled artisan would have had to

conduct undue and excessive experimentation in order to practice the full scope of the claimed invention.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-7 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-14 of U.S. Patent No. 5,888,767A. Although the conflicting claims are not identical, they are not patentably distinct from each other because the conflict claims have overlapping scope of the claimed invention.

The claimed invention in the instant Application is directed to a method for inhibiting a viral DNA replication, particularly by introducing a conditional replication HIV vector (crHIV) into a host cell, wherein the vector carrying one or more nucleotide sequence associated with the anti-viral function, particularly it is disclosed as targeted Ribozyme sequence SEQ ID NO: 3 or 4. The said vector is also constructed with a substitutive mutation at the ribozyme biding site, particularly the possible substitution is disclosed as the vector comprising the sequence of SEQ ID NO: 2, 5, 6, 14, or 16, which enable the vector to escape from the ribozyme reorganization and cleavage. Therefore,

the expression of the ribozyme function as the anti-viral agent to cleavage the wild-type HIV virus and render the inhibition of HIV viral replication targeted at the 3'-nucleotide NUH sequence, wherein the N can be any nucleotide and H can be either A, C, or U. Preferably the NUH sequence comprises a GUC site.

Patent "767" is drawn to a method for expressing a gene in a host cell, which include contacting the host cell with conditional replication human immunodeficiency viral vector comprising a one or more nucleotide sequences encoding a therapeutic antiviral gene. The said gene is a ribozyme enzyme encoded by the SEQ ID NO: 3 or 4, which encode a same nucleotide sequence as it is disclosed in the method for constructing the condition replication HIV vector (crHIV) of the instant Application. The said vector is able to replicate in a host cell only upon complementation of with a wild type HIV, a helper virus or helper vector. However, the wild-type HIV and helper virus or helper vector is sensitive to the presence of the ribozyme expressed by the vector HIV virus and render the inhibition of HIV viral replication targeted at the 3'-nucleotide NUH sequence, wherein the N can be any nucleotide and H can be either A, C, or U. Preferably the NUH sequence comprises a GUC site. In contrast, the vector itself is not sensitive to the ribozyme cleavage because it constructed with a substitutive sequence encoded by SEQ ID NO: 2, 5, 6, 14, 15 or 16. The end of the result associated with the method for expressing the gene product, namely ribozyme inserted in the said conditional replication HIV vector, is the inhibition of the wild-type HIV-1 virus and helper virus or helper vector replication in the host cell.

This is an obvious double patenting because the scopes of the conflict claims are overlapping.

Claims 1-7 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-15 of U.S. Patent No. 5,886,806A. Although the conflicting claims are not identical, they are not patentably distinct from each other because the conflict claims have overlapping scope of the claimed invention.

Patent "806" is drawn to a method of making a human immunodeficiency virus viral vector, which start with a wild-type of the HIV-1 virus, and it is disclosed as the use of the same pNL4-3 strain HIV wild-type virus and procedure as it is disclosed in the

instant Application (See example I through 11 from col. 30 to 42). The said rcHIV vector also comprising a one or more nucleotide sequences encoding a therapeutic antiviral gene. The said gene is a ribozyme enzyme encoded by the SEQ ID NO: 3 or 4. The said vector is also constructed with a substitutive mutation at the ribozyme biding site, the possible substitution is disclosed as the vector comprising the sequence of SEQ ID NO: 2, 5, 6, 14, or 16, which enable the vector to escape from the ribozyme reorganization and cleavage. Those cited sequence in the claims 2-15 encode the same nucleotide sequences as they are disclosed in the method for constructing the condition replication HIV vector (crHIV) of the instant Application. The function of the said vector is able to replicate in a host cell only upon complementation of with a wild type HIV, a helper virus or helper vector. However, the wild-type HIV and helper virus or helper vector is sensitive to the presence of the ribozyme expressed by the vector, whereas the vector itself is not sensitive to the ribozyme cleavage because it constructed with a substitutive sequence encoded by SEQ ID NO: 2, 5, 6, 14, 15 or 16.

Therefore, this is a obvious double patenting since the scopes of the conflict claims are overlapping.

Claims 1-7 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-34 of U.S. Patent No. 6,114,141A. Although the conflicting claims are not identical, they are not patentably distinct from each other because the conflict claims have overlapping scope of the claimed invention.

Patent "141" is drawn to a method of expressing a gene in a host cell, which method comprising contacting the host cell with a conditional replicating virus vector which comprises at least one gene to be expresses and further comprises at least a first nucleotide sequence wherein the conditional replicating vector replicates in the said host only upon complementation with a wild-type virus, a helper virus, or helper vector. The said conditional replicating viral vector is disclosed as a HIV-1 vector derived form the wild-type of HIV-1 pNL4-3 strain (crHIV), which comprises the first sequence include the sequence encoding an anti-HIV ribozyme of SEQ ID NO: 3 or 4. The said vector is also constructed with a substitutive mutation at the ribozyme biding site, the possible substitution is disclosed as the vector comprising the sequence of SEQ ID NO: 2, 5, 6, 14,

or 16, which enable the vector to escape from the ribozyme reorganization and cleavage. The CD4+ T cell transfected with the crHIV comprising the ribozyme exhibit the anti-HIV replication activity when the crHIV transfected cell is challenged with the wild-type HIV-1 virus. Hence, this is an obvious double patenting because the scopes of the conflict claims are overlapping.

Claims 1-7 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-28 of U.S. Patent No.6,168,953B1. Although the conflicting claims are not identical, they are not patentably distinct from each other because the conflict claims have overlapping scope of the claimed invention.

Patent "953" is drawn to a method of increasing the efficiency of an anti-viral agent for its ability to inhibit human immunodeficiency virus in a host cell comprising to administering a HIV viral vector constructed with backbone of a wild-type of the HIV-1 virus, wherein the vector is carried with one or two or multiple anti-HIV ribozyme molecules to cleavage different site of the wild-type of HIV virus and helper virus or helper vector. The ribozyme disclosed in the patent 953 is the same molecule encoded by the SEQ ID NO: 3 or 4 as it is disclosed in the instant Application (See example I through 11 from col. 30 to 42). The said vector is also constructed with a substitutive mutation at the ribozyme biding site, the possible substitution is disclosed as the vector comprising the sequence of SEQ ID NO: 2, 5, 6, 14, or 16, which enable the vector to escape from the ribozyme reorganization and cleavage. Those cited sequence in the claims 2-15 encode the same nucleotide sequences as they are disclosed in the method for constructing the condition replication HIV vector of the instant Application. Therefore, the HIV-1 viral replication is efficiently inhibited by utilization of the said HIV vector.

This is an obvious double patenting because the scopes of the conflict claims are overlapping.

Claims 1-7 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-32 of U.S. Patent No.6,232,120B1. Although the conflicting claims are not identical, they are not patentably distinct from each other because the conflict claims have overlapping scope of the claimed invention.

Patent "120" is drawn to a method for inhibiting HIV-1 viral replication comprising contacting the host cell with a conditional replication HIV vector, wherein the HIV viral vector is constructed with backbone of a wild-type of the HIV-1 virus and it carries with at lease a first nucleotide sequence that encodes a genetic antiviral agent selected from an antisepses molecule, a ribozyme, a nucleic acid decoy, a Tran dominant mutant protein, a single chain antibody, a cytokine and a cellular antigen or receptor that are all adversely affect the wild-type HIV virus but not the viral vector since the viral vector is constructed to contain a mutated gene for the first therapeutic sequence biding site. More preferably, the agent is a ribozyme inserted in the ribozyme expression cassette as a one, two or multiple tandem repeats. The said vector further comprises at least second nucleotide sequence, which confers to said host cell a selective advantage over a second cell infected with a wild-type strain of HIV virus or helper virus or helper vector that is selected from the sequence encoding a multiple resistance gene, a mutant protease gene or a mutant reverse transcriptase. The ribozyme disclosed in the patent 953 is the same molecule encoded by the SEQ ID NO: 3 or 4 as it is disclosed in the instant Application (See example I through 11 from col. 30 to 42). The said vector is also constructed with a substitutive mutation at the ribozyme biding site, the possible substitution is disclosed as the vector comprising the sequence of SEQ ID NO: 2, 5, 6, 14, or 16, which enable the vector to escape from the ribozyme reorganization and cleavage. Those cited sequence in the claims 2, 5, 5, 14 and 16 encode the same nucleotide sequences as they are disclosed in the instant Application.

Although the claimed invention in the instant Application is more broad than the that of the patent NO. 120, the scope of the conflict claims are overlapping.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-7 are rejected under 35 U.S.C. 102(a) as being anticipated by Mautino et al. (Human Gene Therapy Sep. 2000, Vol. 11, pp. 2025-2037)

Mautino et al. teach a method for using an HIV-based lentiviral vector that expresses a 1-kb antisense mRNA directed against the HIV-1 mRNAs containing env. Sequences. The expression of the anti-sense molecule by the HIV-based vector and Mo-MuLV-based vector exhibit a potent inhibition of HIV-1 replication. The nucleotide sequence encoding the anti-sense molecule inserted in the vectors is only designed to target the wild-type HIV-1 but not the vectors. Therefore, the claimed invention is anticipated by the cited prior art.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in-
>
> (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or
>
> (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

Claims 1-7 are rejected under 35 U.S.C. 102(e) as being anticipated by Dropulic et al. (US Patent. No. 6,232,120B1).

The patent "120" disclose a method for inhibiting HIV-1 viral replication comprising contacting the host cell with a conditional replication HIV vector, wherein the HIV viral vector is constructed with backbone of a wild-type of the HIV-1 virus and it carries with at lease a first nucleotide sequence that encodes a genetic antiviral agent selected from an antidsense molecule, a ribozyme, a nucleic acid decoy, a transdominant mutant protein, a single chain antibody, a cytokine and a cellular antigen or receptor that are all adversely affect the wild-type HIV virus but not the viral vector since the viral vector is constructed to contain a mutated gene for the first therapeutic sequence biding site. More preferably, the agent is a ribozyme inserted in the ribozyme expression

cassette as a one, two or multiple tandem repeats. The said vector further comprises at least second nucleotide sequence, which confers to said host cell a selective advantage over a second cell infected with a wild-type strain of HIV virus or helper virus or helper vector that is selected from the sequence encoding a multiple resistance gene, a mutant protease gene or a mutant reverse transcripase. The ribozyme disclosed in the patent 953 is the same molecule encoded by the SEQ ID NO: 3 or 4 as it is disclosed in the instant Application (See example I through 11 from col. 30 to 42). The said vector is also constructed with a substitutive mutation at the ribozyme biding site, the possible substitution is disclosed as the vector comprising the sequence of SEQ ID NO: 2, 5, 6, 14, or 16, which enable the vector to escape from the ribozyme reorganization and cleavage. Those cited sequence in the claims 2, 5, 5, 14 and 16 encode the same nucleotide sequences as they are disclosed in the instant Application. Hence, the claimed invention is anticipated by the cited reference.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-7 are rejected under 35 U.S.C. 102(b) as being anticipated by Dropulic et al. (WO 97/20060A1).

WO 97/20060 disclose a method of making a conditionally replicating viral vector, especially the HIV-1 based retroviral vector, which is characterized by a capacity to replicate only in a host cell that is permissive for replication of said vector in that the said vector comprises at least one nucleotide sequence, the presence, transcription or translation of which nucleotide confers to said vector in a host cell, a selective advantage over a wild-type strain of a virus corresponding to the virus from which said vector was derived or a helper. More preferably, the said conditional replicating HIV-1 vector is disclosed as construct derived from a wild-type of the HIV-1 virus pNL4-3 strain and followed by insertion heamerhead anti-HIV ribozyme sequences in the ribozyme

expression cassette. The said vector is further constructed with a substitutive mutation at the ribozyme biding site, which enable the vector to escape from the ribozyme binding and degradation. The said vector is also disclosed with insertion of other selective gene sequence, such as a multidrug resistance gene to help the further selective over a host cell containing the wild-type virus. The disclosure of the WO 97/20060 also include a method for using the vector to inhibit the wild-type viral replication by contacting the CD4+ host cell with the said condition replication vector, to inhibit the wild-type HIV infection (See entire document, especially the example 1 on pages 56-61 and example 4 on pages 65-69 and claims 1-52). Therefore, the claimed invention is anticipated by the cited prior art.

Claims 1-3 are rejected under 35 U.S.C. 102(b) as being anticipated by Welch et al. (Gene Ther. 1996, Vol. 3, pp. 994-1001).

Welch et al. disclose method for inhibiting the HCV infection by transducing human heptoma cells HepG2 with a retroviral vector carrying two ribozyme molecules, CR2 and CR4 specifically targeted at the HCV RNA 5'UTR and the capsid region but not the retroviral vector itself (See entire document). Therefore, the HCV viral infection is inhibited. Hence, the claimed invention is anticipated by the cited prior art.

Claims 1-3 are rejected under 35 U.S.C. 102(b) as being anticipated by Lieber et al. (J. Virol. 1996, Vol. 70, pp. 8782-8791).

Lieber et al. disclose method for inhibiting HCV viral replication by using an adenovirus vector carrying a nucleotide sequence encoding six hammerhead ribozymes directed against a conserved region of the plus strand and minus strand of the HCV genome but not the adenovirus vector. The expression ribozyme individually or in combination were efficient at reducing or eliminating the respective plus- or minus-strand HCV RNAs expression in culture cells and from primary human hepatocytes obtained from chronic HIV-infected patients (See abstract). Therefore, the claimed invention is anticipated by the cited prior art.

Claims 1-7 are rejected under 35 U.S.C. 102(b) as being anticipated by Venkatesh et al. (P.N.A.S. USA 1990, Vol. 87, pp. 8746-8750).

Venkatesh et al. disclose method for using a replication-defective adenovirus vector that carrying a herpes simplex virus type 1 cytotoxic kinase gene (tk) sequence cloned downstream of the HIV-LTR (Ad-tk) in human cells expressing the HIV-1 transcription activator Tat. Infection of Tat-expression human Hela or Jurkat cells with Ad-tk results in a high-level tk expression, which are not deleterious to the viability of these cells. However, in the presence of the anti-herpetic nucleoside analog ganciclovir, Ad-tk vector became very sensitive to tk gene, and it renders a massive reduction in the viability of these Tat-expressing cell lines. The adenovirus is a replication defective vector, which contains the E1 gene deletion that prevents the vector to become the replication competent virus. Therefore, the claimed invention is anticipated by the cited prior art.

Claims 1-3 and 6-7 are rejected under 35 U.S.C. 102(b) as being anticipated by Lu et al. (Cancer Gene Therapy, 1994, Vol. 1, pp. 267-277).

Lu et al. disclose method for a viral vector carrying an anti-HPV ribozyme to cleavage specifically all transcripts encoding HPV-16 E6 and E7 ORFs. The oligonucleotide corresponding to these ribozymes were synthesized and inserted into a eucaryotic viral vector derived from the non-pathogenic parvovirus, adeno-associated virus. Ribozyme transcription from this vector, termed CRWT7:SV under control of both the highly active Rouse sarcoma virus long terminal repeat and bacteriophage T7 promoters is able to cleavage their cognate targets for the HPV-16 E6 and E7 proteins but no the vector itself. Therefore, the claimed invention is anticipated by the cited prior art.

Claims 1-7 are rejected under 35 U.S.C. 102(b) as being anticipated by Alwine et al. (WO 94/16060A1).

Alwine et al. disclose method for using a conditional-replication incompetent HIV vector mutated on the long terminal repeat (LTR) sequence and in absence of the wild-type Tat protein supplied in trans, wherein a transdominant gene, such as Rev is further mutated to suppress the reversion of replication. In addition, a nucleotide sequence encoding a cytotoxic gene, such as Ricin A subunit is incorporated into the viral vector to

kill HIV-1 infected cells. Therefore, the claimed invention is anticipated by the cited reference.

Claims 1-7 are rejected under 35 U.S.C. 102(b) as being anticipated by Wong-Staal et al. (WO 94/26877A1).

Wong-Staal et al. teach a retroviral vector that comprises a nucleotide sequence encoding an anti-HIV-1 ribozyme and a method for using the ribozyme delivery vector to interfering with or preventing the human immunodeficiency virus infection in the CD4 + human cells. The ribozyme is so designed that is only sensitive for the wild-type HIV-1 virus but not the retroviral vector. The vector also comprises other mutation in its genome so that it cannot produce a replication-competent virus in the host cell (See claims 1-20). Therefore, the claimed invention is anticipated by the cited reference.

Claims 1-7 are rejected under 35 U.S.C. 102(b) as being anticipated Zhou et al. (Gene 1994, Vol. 149, pp. 33-39).

Zhou et al. disclose method for using a conditional-replication incompetent retroviral vector comprising a ribozyme expression cassette, in which two hammerhead ribozymes targeting at the HIV-1 Tat and rev genes are inserted. Introducing the vector into human CD4+ T-lymphocyts results in specifically cleavage of the wild-type of HIV-1 Tat and rev gene produce and inhibiting the wild-type HIV-1 viral replication in the T lymphocyte (See entire document). The claimed invention is therefore, anticipated by the cited reference.

Claims 1-7 are rejected under 35 U.S.C. 102(b) as being anticipated Yu et al. (Virology 1995, Vol. 206, pp. 381-386).

Yu et al. disclose method for using a retroviral comprising a ribozyme expression Cassette, which expresses a hairpin ribozymes targeting at the HIV-1 pol to inhibit the HIV-1 virus replication in CD4+ T cell line. The vector virus is also mutated to render not to produce a replication-competent virus (See entire document). The claimed invention is therefore, anticipated by the cited reference.

Claims 1-7 are rejected under 35 U.S.C. 102(b) as being anticipated Ramezani et al. (Antisense Nucleic Acid Drug Dev. 1996, Vol. 6, pp. 229-235).

Ramezani et al. disclose method for using a moloney murine leukemia virus (MMLV)-derived pUCMoTiN-based retroviral vector that is constructed to comprise a nucleotide sequence that is able to produce a constitutive and Tat-inducible expression of five hammerhead ribozymes targeted against highly conserved sequences of wild-type HIV-1 virus but not the MMLV-derived pUCMoTiN-based vector. Introducing the ribozymes targeting at the HIV-1 Gag (Rz_{Gag}) or RT (Rz_{RT}) into the CD4+ T cells completely inhibit wild-type HIV virus replication. The Ribozyme target against Pro (Rz_{Pro}) and Env (Rz_{Env}) can also completely inhibit virus production (See entire document). The claimed invention is therefore, anticipated by the cited reference.

Claims 1-7 are rejected under 35 U.S.C. 102(b) as being anticipated Lo et al. (Virology. 1992, Vol. 190, pp. 176-183).

Lo et al. disclose method for constructing a ribozyme into a Moloney murine leukemia virus vector. This ribozyme is used to cleavage the RNA of the HIV Tat. Human T-cell lines treated with this moloney murine leukemia virus (MoMLV)-derived vector is able to produce the tat-antisense and the anti-tat ribozyme, and it inhibit the HIV-1 replication upon the cell line is challenged with the wild-type HIV-1 virus (See entire document). The claimed invention is therefore, anticipated by the cited reference.

Claims 1-7 are rejected under 35 U.S.C. 102(b) as being anticipated Dropulic et al. (P.N.A.S. USA, 1996, Vol. 93, pp. 11103-11108).

Dropulic et al. teach to use a conditional replicating HIV-1 (crHIV) vectors carrying anti-HIV ribozyme molecule to interfere with wild-type HIV-1 (wt-HIV) replication and spread. The crHIV vectors are mutated it only replicate in the presence of wt-HIV helper virus. Once the CD4+ T cells contain both wt-HIV and crHIV genomes that the latter are shown to have a selective advantage for packaging into progeny virions because they contain ribozymes that cleave wt-HIV RNA but lack of the ribozyme binding sites, which is susceptible for the cleavage. The crHIV vectors contain a triple anti-U5 ribozyme significantly interfered with wt-HIV replication and spread. The crHIV

vectors were derived form the HIVpNL4-3 molecular clone and comprise either single ribozyme or multiple ribozymes. Human CD4+ T-cell line were transfected with wild-type HIV or this conditional replicating HIV vector carrying either single of multiple ribozymes can inhibit the wt-HIV replication (See entire document, specially the abstract and Fig. 2 on page 11105). The claimed invention is therefore, anticipated by the cited reference.

Claims 1-7 are rejected under 35 U.S.C. 102(b) as being anticipated Dropulic et al. (J. Virol, Vol. 66, pp. 1432-1441).

Dropulic et al. teach to use a genetically modified amphotroic retrovirus, vector containing the anti-HIV hammerhead ribozyme to interfere with wild-type HIV-1 (wt-HIV, pNL4-3) replication and spread. The targets for the hammerhead ribozyme contain the GUCN consensus sequence. Eleven such targets are present in the wild-type HIV-1 genomic RNA. Once the CD4+ T cells transduced with the genetically modified amphotroic retrovirus vector containing the anti-HIV hammerhead ribozyme, the HIV-1 replication is inhibited upon the cells is co-infected with the wild-type HIV-1. However, the vector RNA is not susceptible for the ribozyme cleavage. (See entire document, specially the abstract and Fig. 6 on page 1439). The claimed invention is therefore, anticipated by the cited reference.

Claims 1-7 are rejected under 35 U.S.C. 102(b) as being anticipated Macpherson et al. (Frontiers in Bioscience, June 1999, pp. 497-505).

Macpherson et al. teach a method for using anti-HIV ribozyme that can be carried by various viral vectors to inhibit the HIV-1 or other murine retroviral DNA replications. Especially they explicitly disclose that the target sequence GUCN is designed anti-HIV ribozyme and several viral vector choices, such as moloney murine leukemia virus (MoMLV)-derived vector (MoMLV), gibbon ape leukemia virus (GaLV) or vesicular stomatitis virus (VSV) G-glycoprotein pseudo-typed retroviral vector, adeno-associated viral vector (AAV) and the HIV-1 based lentiviral vector, which are suitable for carrying the anti-HIV-1 ribozyme gene. Macpherson et al. also disclose the update information for

the ribozyme that is in the phase I clinical trail (See entire document). Therefore, the claimed invention is anticipated by the cited prior art.

Claims 1-7 are rejected under 35 U.S.C. 102(b) as being anticipated Sczakiel et al. (Methods in Molecular Biology 1997, Vol. 63, pp. 389-400).

Sczakiel et al. teach a method for using anti-HIV ribozyme that can be carried by retroviral vectors, such as MLV-based vector or HIV-1 based vector to inhibit the HIV-1 replication. Especially they explicitly disclose each steps about how to construct retroviral vector and introduce the ribozyme molecules into the CD4 + T cell as well as measure the inhibition of the HIV-1 replication (See entire document). Therefore, the claimed invention is anticipated by the cited prior art.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bao Qun Li whose telephone number is 703-305-1695. The examiner can normally be reached on 8:00 to 4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 703-308-4027. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Bao Qun Li
April 18, 2002

ALI R. SALIMI
PRIMARY EXAMINER